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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,978	03/22/2001	David A. Schwartz	37154-0753	7639

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DAVID B. WALLER & ASSOCIATES
5677 OBERLIN DRIVE
SUITE 214
SAN DIEGO, CA 92121

EXAMINER
RUSSEL, JEFFREY E

ART UNIT	PAPER NUMBER
1654	14

DATE MAILED: 01/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/815,978	Applicant(s) SCHWARTZ, DAVID A.	
	Examiner Jeffrey E. Russel	Art Unit 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2002 and 05 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *4-21, 31-39, and 45-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,22-30 and 40-44* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. Applicant's election with traverse of the invention of Group I, claims 1-4, 22-31, 34, and 40-44, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Groups I and II should be rejoined because of overlapping subject matter, and that a proper search of Group I would necessarily reveal references relating to claims of Group II. This is not found persuasive because it is not seen that the claims of Groups I and II overlap. The compound of formula I, which is the subject matter of Group I, does not overlap with the compound of Formula II, which forms the basis of Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5-21, 32, 33, 35-39, and 45-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Applicant's election of the species defined by structure in Paper No. 13 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4, 31, and 34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

The Sequence Listing filed July 12, 2001 did not include a statement of no new matter, as required by 37 CFR 1.821(h) and/or 1.825(a).

The compute readable form of the Sequence Listing filed July 12, 2001 was approved by STIC for matters of form.

Correction is required.

3. The drawings filed April 23, 2001 are objected to because in Figure 5, line 1, "aldehyde" is misspelled. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

4. The disclosure is objected to because of the following informalities: At page 4, line 27, "limited" is misspelled. At page 51, line 30, a SEQ ID NO needs to be inserted after the nucleotide sequence. See 37 CFR 1.821(d). Appropriate correction is required.

5. Claims 1, 2, 22-30, and 40-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a derivative thereof" at claim 1, page 57, line 4, is indefinite because it is not clear what degree of structural and/or functional similarity is required to be present a compound of formula I and a second compound in order for the second compound to be considered a "derivative" of the compound of formula I. For example, it is not clear if a derivative must still comprise a hydrazine group, a salt, and/or an aliphatic divalent group. While Applicant's specification at page 9, line 26 - page 10, line 24, describes examples

of derivatives (note Applicant's use of the word "includes" at page 9, line 26), an example is not a definition. The word "derivative" also does not have any art-accepted definition. At claim 1, page 57, line 21, "among" should be changed to "consisting of" so that standard Markush terminology is used. Claim 1 is indefinite because at page 58, line 6, it defines a variable R^{11} which is not used in any of the structural formulas or substituents defined in the claim. It is possible that Applicant instead intended to recite "R^{10}" There is no antecedent basis in the claim for the phrase "the amino moiety or thiol moiety" at claim 29, lines 6-7. Note that line 5 uses the terminology "amino or one thiol reactive moiety" (emphasis added). It is believed that "reactive" should be deleted from line 5.

6. The effective filing date of instant claims 1, 2, 22-30, and 40-44 is deemed to be March 22, 2001, the filing date of the instant application. Instant claims 1, 2, 22-30, and 40-44 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/191,186 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, does not disclose all of the R groups recited in formula I of instant claims 1 and 2.

The effective filing date of instant claim 3 is deemed to be March 22, 2000, the filing date of provisional application 60/191,186. Instant claim 3 is deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of provisional application 60/191,186 because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

8. Claims 1, 2, 22, 25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 93/14779. The WO Patent Application '779 teaches a compound at page 22, Example 5, which anticipates Applicant's compound of formula I in which B is a carboxyl group; R is a cycloalkylene group combined with a $C(R^{10})_2$ group where R^{10} is hydrogen; A is -NH(C=O)-; and X is trifluoroacetate. In Example 6, the compound of Example 5 of the WO Patent Application '779 is reacted with an arginine derivative, which is a synthetic biological molecule, and the product is then conjugated to the amino group of a solid phase resin (which corresponds to Applicant's surface) in Example 7.

9. Claims 1, 2, 22, 25, and 29 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 93/14779 as applied against claims 1, 2, 22, 25, and 29 above, and further in view of Abrams et al (U.S. Patent No. 5,679,778) or Ashkenazi et al (U.S. Patent No. 5,329,028). Compound 5 of the WO Patent Application '779 differs from Applicants' elected species in that compound 5 comprises a trifluoroacetate salt rather than a hydrochloride salt. Abrams et al teach bifunctional linkers in which if a hydrazine group is present, it is present in acid addition salt form. Hydrochloride salts are exemplified. See, e.g., column 2, lines 25-33; column 4, lines 23-24; column 5, lines 22-25; and column 7, lines 34-35. Ashkenazi et al teach bifunctional linkers in which if both hydrazide and maleimide functional groups are present, the hydrazide group is present in the form of a hydrochloride in order to prevent reaction between the two groups (see, e.g., column 6, lines 11-17, and column 9, lines 3-6). It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form compound 5 of the WO Patent Application '779 as a hydrochloride salt rather than as a trifluoroacetate salt because both Abrams et al and Ashkenazi et al disclose hydrochloride salts to be useful salt forms for hydrazide-containing linkers, because the particular salt would not have been expected to affect the reactivity of the hydrazide group of compound 5 with the aldehyde group present in the tBoc-N^g-nitro arginal reactant, and because the substitution of one known functional equivalent for another is prima facie obvious.

10. Claims 1, 2, 22, 23, and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz et al (U.S. Patent No. 5,206,370). Schwartz et al '370 teaches succinimidyl 4-hydrazinobenzoate hydrochloride, which is reacted with the amino groups present in IgG to form a conjugate. See, e.g., column 12, Example 9. The succinimidyl 4-hydrazinobenzoate

hydrochloride of Schwartz et al '370 is deemed to be a derivative of Applicant's claimed compound of formula I in view of their similarity in structure and function. Sufficient evidence of similarity is deemed to be present between the succinimidyl 4-hydrazinobenzoate hydrochloride of Schwartz et al and Applicant's claimed compounds to shift the burden to Applicant to provide evidence that the claimed compounds are unobviously different than those of Schwartz et al '370.

11. Claims 1, 2, 22, and 24-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sytkowski (U.S. Patent No. 5,919,758). Sytkowski teaches 4-(N-maleimidomethyl)cyclohexane-1-carboxyl-hydrazide-HCl, which is used to crosslink erythropoietin molecules (see column 10, lines 8-46). This compound of Sytkowski anticipates Applicant's compound of Formula I in which B is a maleimido group, R is a cycloalkylene group combined with a C(L) group in which L is O; A is a direct bond to R; and X is Cl.

12. Claims 1, 2, 25-27, 30, 41, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Sivam et al (U.S Patent No. 5,521,290). Sivam et al '290 teaches derivatizing a monoclonal antibody with sulfhydryl groups, reacting a hydrazide-containing bifunctional linker of formula I with the derivatized monoclonal antibody, and then reacting the monoclonal antibody hydrazide with ricin A which has been oxidized to form aldehyde groups on its oligosaccharide moieties. See column 5, lines 60-67, and column 18, lines 25-61. With respect to instant claims 25-27, 30, 41, and 44, while Sivam et al '290 does not teach its hydrazide bifunctional linker of formula I in salt form (i.e. does not teach Applicant's HX group), reactant and/or process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. In any event, the non-salt

hydrazide-containing bifunctional linker of formula I of Sivam et al is deemed to be a derivative of Applicant's claimed compound of formula I in view of their similarity in structure and function. Sufficient evidence of similarity is deemed to be present between the non-salt hydrazide-containing bifunctional linker of formula I of Sivam et al and Applicant's claimed compounds to shift the burden to Applicant to provide evidence that the claimed compounds are unobviously different than those of Sivam et al '290.

13. Claims 1, 2, 25-27, 30, 41, and 44 are rejected under 35 U.S.C. 103(a) as being obvious over Sivam et al (U.S. Patent No. 5,521,290) as applied against claims 1, 2, 25-27, 30, 41, and 44 above, and further in view of Abrams et al (U.S. Patent No. 5,679,778) or Ashkenazi et al (U.S. Patent No. 5,329,028). As noted above, Sivam et al do not teach their bifunctional linker in salt form. Abrams et al teach bifunctional linkers in which if a hydrazine group is present, it is present in acid addition salt form (see, e.g., column 2, lines 25-33). Ashkenazi et al teach bifunctional linkers in which if both hydrazide and maleimide functional groups are present, the hydrazide group is present in the form of a hydrochloride in order to prevent reaction between the two groups (see, e.g., column 6, lines 11-17, and column 9, lines 3-6). It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the bifunctional linker of Sivam et al in the form of a hydrochloride salt because both Abrams et al and Ashkenazi et al teach the desirability of forming hydrazide-containing bifunctional linkers in salt form and because Ashkenazi et al teaches that such bifunctional linkers in salt form would have the additional desirable property of not self-polymerizing.

14. Claims 1, 2, 25, 30, 41, 42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated Berninger et al (U.S. Patent No. 5,856,571). Berninger et al '571 teaches reacting a

first hydrazide-containing linker having the structure at column 5, lines 22-24, with biotin to form a hydrazide-containing biotin conjugate (see column 16, lines 17-25, formula V). The conjugate is then reacted with an antibody which has been subjected to periodate oxidation so as to form aldehyde groups on its oligosaccharide substituents (see column 16, line 49 - column 17, line 12). With respect to instant claims 25, 30, 41, 42, and 44, while Berninger et al '571 does not teach its hydrazide-containing linker in salt form (i.e. does not teach Applicant's HX group), reactant and/or process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. In any event, the non-salt hydrazide-containing linker of Berninger et al '571 is deemed to be a derivative of Applicant's claimed compound of formula I in view of their similarity in structure and function. Sufficient evidence of similarity is deemed to be present between the non-salt hydrazide-containing linker of Berninger et al '571 and Applicant's claimed compounds to shift the burden to Applicant to provide evidence that the claimed compounds are unobviously different than those of Berninger et al '571.

15. Claims 25, 26, 28, 40, and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Whelihan (U.S. Patent No. 6,238,860). Whelihan '860 teaches polypeptides which are synthesized with a Glu-Gly-Gly-Gly-Ser spacer sequence, modified with a hydrazide functionality, and then immobilized on an aldehyde-functional methacrylate resin support. See column 14, lines 12-52. Whelihan '860's spacer sequence corresponds to Applicant's B-R-A groups of formula I: the carboxyl group of the Glu residue corresponds to B which is reactive with an amino group; the remainder of the spacer sequence corresponds to R which is a combination of $C(R^{10})_2$, $N(R^{10})$, and C(L) groups where L is O; and A is a direct bond to R.

While Whelihan '860 does not teach an isolated hydrazide-containing linker corresponding to Applicant's formula I, reactant and/or process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. Note also that instant claim 25 does not require the compound of claim 1/formula I to be bound to the natural or synthetic biological molecule through the B group present in the compound of claim 1/formula I.

16. Claims 1, 2, 22, 25, 26, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by the Heindel et al article (Bioconj. Chem., Vol. 2, pages 427-430). The Heindel et al article teaches a heterobifunctional linker (see Scheme II, compound 1), which corresponds to Applicant's compound of formula I in which B is a thiol reactive moiety; R is a combination of a $C(R^{10})_2$ group and a C(L) group where L is O; A is a direct bond to R; and X is Cl. The heterobifunctional linker is used to bind a monoclonal antibody to a polyaldehyde dextran by first reacting the linker with the polyaldehyde dextran and then reacting the monoclonal antibody. See, e.g., the Abstract and page 429, column 1, first full paragraph. With respect to instant claim 44, process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

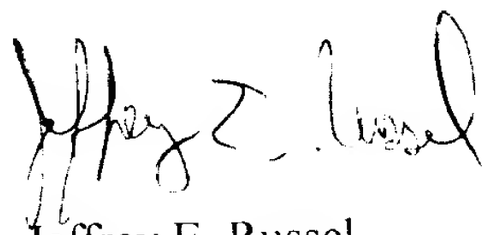
17. Claims 1, 2, 22, 25-27, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by the Zara et al article (Analytical Biochemistry, Vol. 194, pages 156-162). The Zara et al article teaches a heterobifunctional crosslinker TPCH (see Figure 1 and page 157, column 1, first full paragraph), which corresponds to Applicant's compound of formula I in which B is a thiol reactive moiety; R is a combination of $C(R^{10})_2$ groups and a C(L) group where L is O; A is a direct bond to R; and X is Cl. The heterobifunctional linker is used first to modify a periodate-

treated antibody and then to react pyridyl disulfide-derivatized barley toxin with the modified antibody. See, e.g., the Abstract. With respect to instant claim 44, process limitations do not impart patentability to process-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

18. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Compound 5 of the WO Patent Application 93/14779 is deemed to be the closest prior art of record to the compound recited in instant claim 3. Compound 5 differs from the claimed compound in that compound 5 does not comprise a N-hydroxysuccinimidyl group, and comprises a trifluoroacetate rather than a hydrochloride salt. There is not deemed to be any motivation in the prior art of record to modify compound 5 of the WO Patent Application '779 so that it comprises a N-hydroxysuccinimidyl group because such a modification would render the compound more reactive towards amino groups, and this increase in activity would interfere with achieving the intended product of Example 6 of the WO Patent Application '779 because of the presence of the amino group in the tBoc-N^g-nitro arginal reactant.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

January 8, 2003